REMARKS

Restriction Requirement

Claims 4-8, 10-13 and 18-51 are considered to be withdrawn as non-elected claims. Claims 34-51 have been cancelled, without prejudice to or disclaimer of the subject matter therein. Applicants expressly reserve the right to pursue the subject matter of the cancelled claims in a divisional application without the need to file a terminal disclaimer.

Claims 4-8 and 10-13 are presently retained in the event that the linking Claim is found to be allowable.

Claims 18-33 are presently retained, pursuant to Applicants' right to amend Claims 18-33 be commensurate in scope with the elected product claims, and to request that such amended method that depend from or otherwise include all the limitations of any allowable product claims be rejoined and examined for patentability. In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1996); In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995).

Objection to the Specification and Rejection of Claims 16-17 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 16-17 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. The Examiner contends that the specification fails to provide sufficient evidence that the claimed formulations would comprise effective vaccine formulations. Specifically, the Examiner contends that the vaccine arts are such that no formulations comprising an antigen, IL-15 and an anti-IL-2 antibody which induce effective immunity are known in the art. The Examiner states that because vaccines are intended for *in vivo* therapy, the disclosure must be enabling for *in vivo* use. The Examiner addresses particular concerns to the embodiments of a tumor antigen and an HIV antigen. Specifically, the Examiner cites references which are reported to contain comments regarding the failure or disappointing results of same cancer vaccines, viral vaccines, and parasite vaccines. The Examiner therefore contends that in the absence of any data showing an actual vaccine and in view of the alleged unpredictability in the art regarding vaccines, the claims are not enabled.

Applicants traverse the Examiner's rejection of Claims 16-17 under 35 U.S.C. § 112, first paragraph. The Examiner points to several different examples of vaccines that have proven to be disappointing or failures. However, the Examiner does not acknowledge the abundance of other vaccinating antigens that have been demonstrated to be successful. The present inventors have provided a novel adjuvant for the stimulation of memory T cells, the effect of which has been demonstrated. Therefore, to combine the adjuvant with a vaccinating antigen for use as a vaccine is enabled, as there are many vaccinating antigens already known in the art that could be used with the adjuvant of the claimed invention to provide a vaccine that elicits an immune response against the vaccinating antigen.

Vaccination has been known in the art for years, and there are of course multiple well known and effective vaccinating antigens in use in the clinic everyday against such infectious diseases as tetanus, pertussis, poliomyelitis, measles, mumps, rubella, influenza, pneumonia, hepatitis, varicella zoster infection (chicken pox), etc. (e.g., see Santoli et al.; 2004; *Pediatrics* 113(6 Suppl):1959-64). Many of these antigens could be used in conjunction with the claimed adjuvant to provide a vaccine, for example. The specification teaches that a vaccinating antigen, when administered to an animal with the adjuvant of the invention, elicits an immune response against the same or similar antigens in the animal. The specification does not teach that a vaccine *must* cure or prevent a disease; instead, increasing memory T cells in the animal can have some benefit to the animal even though disease is not cured or prevented entirely. Clearly, some diseases will provide greater challenges to vaccine development than others, but the Examiner seems to select examples of negative results without acknowledging the many positive results in the art. Indeed, because the adjuvant of the present invention is directed to enhancing T cell memory, it is particularly suited to use with antigens against which immunization presents more of a challenge (e.g., see Background of the specification, page 2, lines 10-15).

Moreover, even among the Examiner's examples, Applicants submit that enablement and utility of vaccines is shown despite generally disappointing results. For example, even a delay in tumor growth as a result of a tumor vaccine, using the Examiner's example with regard to Bodey et al., can provide a patient with some benefit. The Examiner states that selection for the most aggressive tumor cells would likely exacerbate disease in the long run, although this statement does

not seem to come from Bodey et al., but rather from the Examiner. In contrast, Bodey et al. recognize that cancer vaccines, even if unable to eradicate a tumor, still have use as an adjunct to other traditional therapies and other immunotherapeutical approaches (see abstract and last paragraph of Discussion of Bodey et al.). The fact that many cancer vaccines had not been demonstrated to *eradicate* tumor growth as hoped is not a demonstration that the vaccine was not operable or useful, or that using a cancer antigen in conjunction with the *claimed adjuvant* would not have some utility, even as an adjunct to traditional therapy by delaying tumor growth.

With regard to the reference of Cohen (2002), the Examiner contends that it is not even known whether a CTL response against a virus is capable of protection. However, the Cohen reference teaches that the HIV vaccine trial was not funded because the CTL responses were lower than hoped for, not because the vaccine was deemed not to provide protection (it does not appear that the trial reached this stage of analysis). It is also noted in Cohen that a larger study of a similar vaccine would proceed in Thailand (where NIH funding would not directly dictate the progress) and that another similar vaccine in development by Merck was scheduled to begin. Therefore, it is submitted that this reference does not support the Examiner's argument that the present invention is not enabled. Applicants are not aware that the role of CTL responses in controlling viruses is or was in doubt and it is believed that the importance of CTL responses in controlling viral infection continues to be demonstrated (e.g., Spearman, 2003, *Curr. HIV Res.* 1(1):101-120; abstract attached).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 16-17 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-3, 9 and 14-15 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-3, 9 and 14-15 under 35 U.S.C. § 103, contending that these claims are unpatentable over Zhang et al. in view of Lenardo Specifically, the Examiner contends that Zhang et al. teaches that IL-15 causes the "strong and selective" stimulation of memory T cells. The Examiner admits that Zhang et al. do not teach the use of IL-15 in an adjuvant formulation or the inclusion of anti-IL-2 in such formulation. The Examiner cites Lenardo as providing a teaching that IL-2 is required for the programmed cell death of mature (antigen activated)

T cells. It is then asserted that it would be *prima facie* obvious to one of ordinary skill in the art to arrive at the claimed invention given the combined teachings of Zhang et al. and Lenardo The Examiner asserts that one would be motivated to combine IL-15 with anti-IL-2 because "it would reduce the programmed cell death of the T cells stimulated by the IL-15", to produce a vaccine adjuvant for the induction of an improved and long lasting immune response.

Applicants traverse the Examiner's rejection of Claims 1-3, 9 and 14-15 under 35 U.S.C. § 103. For a *prima facie* case of obviousness to be established, the combination of references must teach each and every element of the invention; there must be a motivation to combine the references to arrive at the invention; and there must be an expectation of success to arrive at the claimed invention from the combination. Applicants submit that a *prima facie* case of obviousness has not been established and that the combination of references does not teach or suggest the present invention.

First, the combination of references does not teach each and every element of the invention. As the Examiner acknowledges, Zhang et al. do not teach an adjuvant composition comprising IL-15 or the inclusion of anti-IL-2 in such a formulation. Lenardo do not teach or suggest any adjuvant formulation comprising IL-15 or an anti-IL-2 compound.

Second, contrary to the Examiner's assertion, the combination of references fails to provide any motivation to arrive at the present invention and in fact, Applicants submit that Zhang et al. represents a *teaching away* from the claimed invention. Referring first to Zhang et al., while Zhang et al. teach that IL-15 causes the strong and selective stimulation of memory-phenotype $CD8^+$ T cells *in vivo*, Zhang et al. teach that IL-2 caused minimal or insignificant stimulation of memory-phenotype $CD4^+$ and $CD8^+$ T cells (e.g., see "T Cell Turnover In Vivo After IL-15 Injection"). Therefore, Zhang et al. do not teach or suggest that IL-2 should be inhibited and in fact teach that IL-2 causes a mild stimulation of the memory phenotype. Given these teachings, there is absolutely no suggestion or motivation provided by Zhang et al. that IL-2 should be *blocked* with regard to the stimulation of memory T cells. At a minimum, one of skill in the art would do nothing with regard to IL-2 based on the teachings of Zhang et al., and Applicants further argue that if one of skill in the art did contemplate the teachings of Zhang et al. with regard to IL-2, one would *provide* IL-2 to try to achieve the minimal stimulation of memory phenotype observed by Zhang et al., rather than block

IL-2. Thus, Zhang et al. can be viewed as a *teaching away* from the presently claimed invention, or at least provides absolutely no motivation to be combined with Lenardo as the Examiner has done. With regard to Lenardo, this reference is directed to the observation that mature T cells that have been previously exposed to IL-2 undergo apoptosis upon exposure to antigen stimulation. However, this teaching is directed to the effects of IL-2 on activated, mature T cells, and does not provide any teaching of the effect of IL-2 on the proliferation and survival of *memory* T cells, particularly outside of the context of antigen stimulation (i.e., under antigen independent conditions). Therefore, there is no motivation provided by the teachings of Lenardo et al. to combine this reference with Zhang et al. and arrive at the present invention. Indeed, referring again to the discussion of Zhang et al. above, where IL-2 provided a mild stimulatory or no significant effect on cells of a memory phenotype, one viewing the teachings of Lenardo and looking at Zhang et al. would determine that the observed effect of IL-2 on activated mature T cells versus memory T cells is different, and would thus find no motivation to combine the teachings. There is simply no motivation provided by the combination of references to produce an adjuvant formulation whereby IL-15 is stimulated and IL-2 is inhibited.

Third, with respect to the expectation of success, based on the teachings of Zhang et al. and Lenardo et al. discussed above, based on each of Zhang et al. and Lenardo, given that Lenardo is not directed to memory T cells and Zhang et al. describes only a mild *stimulatory* effect of IL-2 on memory phenotype, one is not provided with any expectation of success at providing an adjuvant formulation whereby IL-15 is stimulated and IL-2 is inhibited.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 9 and 14-15 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the Examiner's concerns as set forth in the April 27 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has additional questions regarding Applicants' position, he is respectfully encouraged to contact the below-named agent at (303) 863-9700 to expedite prosecution of the claims.

Respectfully submitted,

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☐ 1: Pediatrics. 2004 Jun;113(6 Suppl):1959-64.

Insurance status and vaccination coverage among US preschool children.

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BACKGROUND: Insurance status has been shown to have an impact on children's use of preventive and acute health services. The objective of this study was to determine the relationship between insurance status and vaccination coverage among US preschool children aged 19 to 35 months. METHODS: We linked data from 2 national telephone surveys, the National Immunization Survey and the National Survey of Early Childhood Health, conducted during the first half of 2000. Children were considered up to date (UTD) when they had received at least 4 diphtheria-tetanus-acellular pertussis/diphtheria-tetanus-pertussis vaccines, 3 poliovirus vaccines, 1 MMI vaccine, 3 Haemophilus influenza vaccines, and 3 hepatitis B vaccines at the time the interview was conducted. RESULTS: Among the 735 children in ou study sample, 72% were UTD. The vast majority (94%) reported some type of health insurance at the time of the survey. Children with private insurance were more likely to be UTD (80%) than those with public insurance (56%) o no insurance (64%). In a multivariate analysis that controlled for child's race/ethnicity; household income; maternal age/marital status/educational level; location of usual care; and Special Supplemental Nutrition Program fo Women, Infants, and Children participation, insurance was no longer an independent predictor of vaccination. CONCLUSIONS: The disparity in vaccination coverage among publicly, privately, and uninsured children is dramatic, underscoring its importance as a marker for underimmunization, despite the multivariate findings. The Vaccines for Children Program, a partnership between public health and vaccination providers who serve uninsured children and those enrolled in Medicaid, is well suited to target an improve vaccination coverage among these vulnerable children.

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☐ 1: Curr HIV Res. 2003 Jan;1(1):101-20.

HIV vaccine development: lessons from the past and promise fo the future.

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The global HIV epidemic continues to expand, exceeding previous predictions and causing tremendous suffering. An effective vaccine represent the best hope to curtail the HIV epidemic. The past fifteen years of HIV vaccine clinical trials have not identified an ideal HIV vaccine, but have provided many valuable lessons that contribute to the current generation of promising HIV vaccine regimens. An enhanced understanding of HIV and SIV immunopathogenesis has facilitated the design of vaccination regimens that elicit specific immune responses and effector mechanisms. Intensive investigation of recombinant gp120 subunit vaccines has revealed a previously unexpected complexity in eliciting neutralizing antibodies that are active against primary isolate viruses. The importance of CD8+ CTL responses in controlling HIV and SIV viremia has led to a series of vaccine candidates that effectively induce these responses. Proof that vaccination can prevent SIV/HIV disease has now been obtained in simian models of AIDS. A number of promising HIV vaccine regimens are currently being evaluated in human trials, and the pipeline of new vaccine vectors and combination regimens appears robust. Although challenges to the development of a safe and effective global HIV vaccine remain, the outlook for HIV vaccines in the future is bright.

Publication Types:
- Review
- Review, Tutorial

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